REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

In recent years, a radical treatment for allergic disease has been a hyposensitization therapy in which an allergen per se is administered by a conventional injection at stepwise increased doses over a long period of time so as to decrease allergen-specific immunoreactions. However, it has been noted that the allergens used in this therapy retain reactivity with the IgE antibody bound to mast cells which cause allergic symptoms and, therefore, may result in problematic side effects, such as anaphylactic shock.

Recently, a peptide immunotherapy involving the administration of an allergen-derived T-cell epitope peptide has drawn much attention. The action mechanism thereof is presumed to involve the induction of unresponsiveness or deletion of allergen-specific type 2 helper T cells. T-cell epitope peptide immunotherapy is quite safe, because it generally involves neither B cell epitopes, which cause allergic reactions, nor binding to the allergen-specific IgE antibody; as a result, it minimizes the harmful side effects observed in conventional hyposensitization therapy.

T-cell epitope peptides derived from Japanese cedar pollinosis allergen show a high reactivity toward specific T cells, suggesting a capability thereof to induce T-cell unresponsiveness through oral administration. Although, from these facts, T-cell epitope peptide has been expected to be used as a peptide vaccine for the treatment of Japanese cedar pollinosis, an actual application form has remained undeveloped.

To date, a method for actually accumulating an allergen-specific T-cell epitope in a useful plant or a useful plant comprising such an epitope accumulated therein has been hitherto unknown.

The present invention is directed to overcoming this deficiency in the art.

The objection to claims 4 and 41 is respectfully traversed in view of the above amendments.

The objection to claims 9, 10, 20, 30-33, 44, and 45 is respectfully traversed in view of the above amendments.

The rejection of claim 21 under 35 U.S.C. 112 (2nd para.) as being incomplete for omitting essential elements is respectfully traversed in view of the above amendments.

The rejection of claims 4, 5, 7-10, 20, 21, 26, 28, 30, 32, 41, and 44 under 35 U.S.C. 103(a) for obviousness over Alli et al., "Pharming Vaccines for Hepatitis and Cytomegalovirus: Towards the Development of Multivalent and Subunit Vaccines for Oral Delivery of Antigens," *Phytochemistry Reviews* 1:55-66 (2002) ("Alli") in view of Hirahara et al., "Preclinical Evaluation of an Immunotherapeutic Peptide Comprising 7 T-cell Determinants of Cry j 1 and Cry j 2, the Major Japanese Cedar Pollen Allergens," *J Allergy Clin Immunol* 108:94-100 (2001) ("Hirahara") is respectfully traversed.

Alli discusses a plant based high fidelity vaccine production system being developed with emphasis on producing antigens capable of being orally delivered in multivalent or subunit plant packets. Alli teaches that plant-based edible vaccines may provide an attractive, safe, and inexpensive alternative to conventional vaccine production. Alli teaches that several antigens from different infectious agents have been successfully produced in plants (see last paragraph on page 56) and discusses hepatitis B virus ("HBV") nucleocapsid expression in edible carrot and rice plants (see page 59).

The PTO acknowledges that Alli fails to teach an allergen-specific T-cell epitope and has cited Hirahara for its teaching of the oral administration of allergen-specific T cell epitopes from the Cry j 1 and Cry j 2 protein from Japanese cedar pollen.

Hirahara teaches the recombinant production of peptides that are allergen-specific T-cell epitopes from the Cry j 1 and Cry j proteins from Japanese cedar pollen.

The PTO asserts that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to produce vaccines for oral delivery of antigens, as taught by Alli, to express the Cry j 1 or Cry j 2 epitopes, as taught by Hirahara. Central to the PTO's position is the suggestion that pathogenic epitopes, such as the immunoprotective viral antigens utilized by Alli, may be readily exchanged for immunotherapeutic allergy epitopes, such as the Cry j 1 and Cry j 2 proteins described by Hirahara, to arrive at the invention of the pending claims. Applicants respectfully disagree.

Firstly, applicants submit that the proposed combination of Alli and Hirahara is rife with unpredictability, undermining any "reasonable expectation of success" necessary for establishing a *prima facie* case of obviousness. In this case, applicants respectfully submit that

the teachings of the prior art not only fail to provide a sufficient basis for a reasonable expectation of success but also fail to account for applicants' unexpected success. As stated in *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986), the prior art can be modified or combined to reject claims as *prima facie* obvious only so long as there is a reasonable expectation of success. While obviousness does not require absolute predictability, at least some degree of predictability is required. Thus, evidence showing there was no reasonable expectation of success can support a conclusion of nonobviousness. *See In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976).

While expressing an antigen peptide gene using a rice glutelin (Gt3) promoter and accumulating it within the rice seed is arguably suggested by the prior art, the mere *expression* of a gene is pointless. Rather, practical application requires *accumulating* the desired antigen within rice seeds at a sufficiently high level. It is precisely this – a practically usable allergy vaccine that provides for high level accumulation of the antigen of interest – that is the subject of the present invention and is not fairly suggested by the prior art of record. In particular, prior to the present invention, there were no reports of high accumulation (3-4% of total proteins; 50 μg per one rice grain) of an artificial hybrid peptide with sequentially linked T cell epitopes. It is important to note that the expression and accumulation of artificial genes cannot be predicted beforehand until the gene is actually expressed. In the context of the present invention, in order to obtain a high expression of an artificial gene, applicants synthesized the gene using a codon that is used in high frequency in rice seeds. This codon frequency is characteristic of rice seeds and is clearly different from other tissues, such as leaves and stems. However, although the T cell hybrid peptide is transcribed in the leaves, stem, and root of other plants, it surprisingly does not accumulate there. Even in rice leaves, it cannot accumulate and is quickly degraded. This stands in contrast to expressing antigens, or parts thereof, that exist in nature. Applicants submit that the requisite high accumulation of an artificial hybrid peptide with sequentially linked T cell epitopes in rice seeds cannot be predicted from the prior art, particularly that pertaining to the expression of natural rather than synthetic peptides.

Even if the PTO had established a *prima facie* case of obviousness, which it has not, such a *prima facie* case is rebutted by significant indicia of non-obviousness. Examples of rebuttal evidence include evidence of secondary considerations, such as "commercial success, long felt but unsolved needs, [and] failure of others" (*See e.g., Graham v. John Deere Co.*, 383

U.S. 1, 148 USPQ 459 (1966)); evidence of the state of the art and the level of skill in the art (*See e.g., In re Oelrich,* 579 F.2d 86, 198 USPQ 210 (CCPA 1978)); evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art; (*See In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 Fed. Cir. 1990).

Here, applicants' transfected rice seeds possess surprising thermostability, with no alteration in the T-cell epitope-linked peptide being observed before and after a 20-min heat treatment of transformant seeds and even being stably present after cooking the rice. See p. 3, lines 14-16, as well as Example 5 and Figure 8 of the present application. In the case of an allergy vaccine (e.g., a T cell epitope), thermostability is indeed a major discovery. Unlike Alli's transformed seeds, which must be ground to permit oral delivery of the pathogenic antigens harbored therein, applicants' claimed invention permits oral delivery of allergens in a more conventional and, indeed, gastronomically acceptable way. Furthermore, the vaccine of the present invention has the characteristic of accumulating mostly in protein granules I (PB-I) where prolamin accumulates. This accumulation site is important in that it makes it hard for the vaccine to be digested by stomach acids and, therefore, facilitates efficient delivery to immune tissues of the intestinal canal.

Applicants respectfully request reconsideration in view of the high degree of unpredictability in the art (which precludes the requisite reasonable expectation of success) and the unexpected superiority of the claimed invention. Accordingly, the obviousness rejection based on the combination of Alli and Hirahara is improper and should be withdrawn.

The rejection of claims 6, 27, 29, 31, 33, and 45 under 35 U.S.C. 103(a) as being unpatentable over Alli in view of Hirahara, U.S. Patent No. 5,990,384 to Bagga et. al., ("Bagga"), and Kim et al., "Improvement of Nutritional Value and Functional Properties of Soybean Glycinin by Protein Engineering," *Protein Engineering* 3:725-731 (1990) ("Kim") is respectfully traversed.

Bagga teaches materials and methods for transformed plants and plant tissues that are capable of expressing high levels of stable proteins which are localized as protein bodies within the plant cell.

Kim teaches that glycinin is one of the predominant storage proteins of soybean. To improve its functional properties (heat-induced gelation and emulsification) and/or nutritional value, Kim discloses that the $A_{1a}B_{1b}$ proglycinin subunit was modified on the basis of genetically

variable domains suggested from the comparison of amino acid sequences of glycinin-type globulins from various legumes and nonlegumes and the relationships between the structure and the functional properties of glycinin. Nucleotide sequences corresponding to each of the variable domains were deleted from the cDNA encoding the $A_{1a}B_{1b}$ proglycinin, and a synthetic DNA encoding four continuous methionines was inserted into the cDNA region corresponding to each of the variable domains. Expression plasmids carrying the modified cDNAs were constructed and expressed in *Escherichia coli* strain JM105. The expressed proteins exhibited functional properties superior to those of the native glycinin from soybean which establishes the possibility of creating theoretically designed novel glycinins with high food qualities.

The PTO asserts that at the time the present invention was made, it would have been obvious to combine the teachings of Alli and Hirahara, as noted above, with the methods for transforming plants, as taught by Bagga, and methods for inserting a peptide into a variable region of a storage protein, as taught by Kim, to arrive at a method of expressing a Cry j epitope as a fusion with a storage protein by inserting the Cry j peptide into a variable region of a storage protein.

Neither Bagga nor Kim overcomes the above-noted deficiencies of Alli and Hirahara. Moreover, applicants submit that the utilization of a carrier for storage proteins, or as a fusion protein, is indeed critical as it affords the resulting combination with unique and unexpected properties. In particular, prior to the present invention, no one had introduced a 100-200 amino acid residue peptide like Japanese cedar pollen allergen Cry j1 or Cry j2 and managed to successfully and stably accumulate such a long peptide. Thus, in this sense the claimed invention is a substantial discovery. Furthermore, by inserting the long peptide into a glutelin variable region and expressing it, the protein gets accumulated in PB-I as a glutelin precursor. This is particularly advantageous in the context of inducing immune tolerance, where glutelin is produced as a precursor, and is processed after being transported to PB-2, which is where glutelin is conventionally accumulated, and is then digested into an acid subunit and a basic subunit. By inserting the epitope, it gets accumulated as a precursor, which, in turn, affords it with novel and unexpected advantages over the prior art.

Accordingly, the obviousness rejection based on the combination of Alli, Hirahara, Bagga, and Kim is improper and should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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